

FILE 'MEDLINE, CAPLUS, BIOSIS, AGRICOLA' ENTERED AT 14:25:55 ON 15 APR
2004

L1 110704 S HETEROCYCLIC
L2 339 S P450BM-3 OR P450BM3 OR P450BM
L3 3 S L2 AND L1
L4 2 DUP REM L3 (1 DUPLICATE REMOVED)
L5 0 S P450 NEAR3 BM
L6 370 S P450 AND MEGATERIUM
L7 5 S L6 AND L1
L8 3 DUP REM L7 (2 DUPLICATES REMOVED)
L9 574 S P450 AND L1
L10 80 S L9 AND OXIDATION
L11 35 S L10 AND AROMATIC
L12 23 DUP REM L11 (12 DUPLICATES REMOVED)
L13 689 S PAH AND P450
L14 901 S PAH AND P450?
L15 1 S L14 AND P450BM-3
L16 1 S L14 AND P450BM?

L12 ANSWER 7 OF 23 MEDLINE on STN DUPLICATE 4
 AN 1998372714 MEDLINE
 DN PubMed ID: 9705755
 TI Activation of **heterocyclic aromatic** amines by rat and human liver microsomes and by purified rat and human cytochrome **P450 1A2**.
 AU Turesky R J; Constable A; Richoz J; Varga N; Markovic J; Martin M V; Guengerich F P
 CS Nestle Research Center, Nestec Ltd., Vers-chez-les-Blanc, 1000 Lausanne 26, Switzerland.. TURESKY@CHLSNR.NESTRD.CH
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 R35 CA44353 (NCI)
 SO Chemical research in toxicology, (1998 Aug) 11 (8) 925-36.
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 LA English
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 EM 199809
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 AB The dietary mutagens 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) are activated to genotoxins by rat and human liver cytochrome **P450** (**P450**) 1A1- and 1A2-mediated N-oxidation. Immunoquantitation of 51 human liver samples revealed a wide range in **P450 1A2** expression (10-250 pmol/mg of microsomal protein, median 71 pmol/mg), with 39% of the livers containing >100 pmol/mg of protein. There was no evidence for expression of **P450 1A1** (<1 pmol/mg of protein). **P450 1A2** levels were correlated to MeIQx and PhIP N-oxidation rates (r = 0.83, 0.73, respectively). In male Fischer-344 and Sprague-Dawley rats, hepatic **P450 1A2** ranged from 5 to 35 pmol/mg of protein, while **P450 1A1** was <1 pmol/mg. Animal pretreatment with 3-methylcholanthrene, beta-naphthoflavone, or polychlorinated biphenyls (PCB) resulted inasmuch as 340-fold and >1000-fold induction of **P450 1A2** and 1A1, respectively, and a 220-fold increase in N-oxidation activity. Approximately 20% of the human samples were as active in N-oxidation and conversion of MeIQx to bacterial mutagens as microsomes of PCB-pretreated rats [3-4 nmol of NHOH-MeIQx formed min⁻¹ (mg of protein)⁻¹]. In contrast, microsomes from PCB-treated rats displayed higher rates of PhIP N-oxidation and activation to mutagens than the most active human liver microsomes [8-24 vs 2-4 nmol of HNOH-PhIP formed min⁻¹ (mg of protein)⁻¹]. Recombinant human **P450 1A2** showed catalytic efficiencies of MeIQx and PhIP N-oxidation that were 10-19-fold higher than purified rat **P450 1A2**. Cytochrome **P450 1A2** expression in rodent and human liver tissue varies greatly and there are considerable differences between the enzymes in the two species in the activation of some **heterocyclic aromatic** amines, which must be considered when assessing human health risk.